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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 4 : A61M 5/32, B29B 17/00

A1

(11) International Publication Number: WO 87/ 03495

(43) International Publication Date: 18 June 1987 (18.06.87)

(21) International Application Number: PCT/US86/02668

(22) International Filing Date: 11 December 1986 (11.12.86)

(31) Priority Application Number: 809,235

(32) Priority Date: 16 December 1985 (16.12.85)

(33) Priority Country: US

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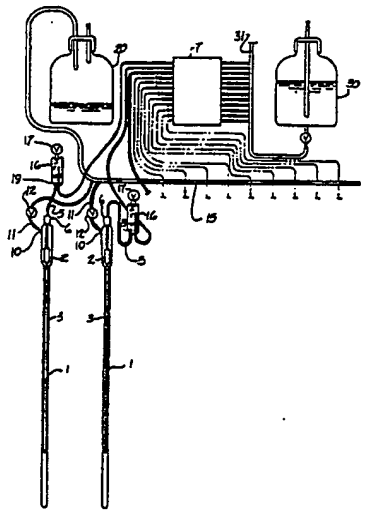
(81) Designated States: AT (European patent), AU, BE (European patent), BR, CH (European patent), DE (European patent), FI, FR (European patent), GB (European patent), IT (European patent), JP, LU (European patent), NL (European patent), NO, SE (European patent).

Published
With international search report.

(54) Title: ANTIMICROBIAL CATHETER AND METHOD

(57) Abstract

A medical device (3) having impregnated therein a combination of antimicrobials (30) by the action of a swelling agent and a method of impregnating a medical device (3) with a combination of antimicrobials (30).



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ANTIMICROBIAL CATHETER AND METHOD

Background of the Invention

Implanted medical devices which involve catheters, valves, molded parts, etc., and which must reside totally or partially within the human body for relatively long periods of time have historically been plagued with the problem of sepsis. Examples of this group of devices include hydrocephalus shunts, parenteral feeding catheters and foley catheters. In some situations, extensive colonization of bacteria on the surfaces of the catheter or other part of the device can produce serious patient problems including infection and even the need to replace the implanted devices.

A considerable amount of attention and study has been directed to attempting to moderate or eliminate sepsis resulting from such colonization by the use of antimicrobial agents, such as antibiotics, bound to the surface of the materials employed in such devices. In such attempts the objective has been to produce a sufficient bacteriostatic or bacteriocidal action to prevent colonization, and therefore avoid sepsis.

These prior attempts have utilized a wide variety of antimicrobial agents, methods for their application and adherence on a wide variety of substrate materials, including silicone elastomers, polytetrafluoroethylene, polyesters, polyethylene, and latex rubber.

Exemplary of the extensive investigation into this problem by researchers are the following publications, which are incorporated herein by reference.

BAYSTON, R., and MILNER, R.D.G., "Antimicrobial Activity of Silicone Rubber Used in Hydrocephalus Shunts, after Impregnation with Antimicrobial Substances" J Clin Pathol 1981, 134:1057-1062.

BAYSTON, R., "Effect of Antibiotic Impregnation on the Function of Slit Valves Used to Control Hydrocephalus" Z. Kinderchir. Band 31, Heft 4, December 1980.

BAYSTON, R. et al, "A Model of Catheter Colonization In Vitro and its Relationship to Clinical Catheter Infections", Journal of Infection, 1984, 9, 271-276.

BAYSTON, R. (1977b): "The antibacterial effects of impregnated silastic and its possible applications in surgery." J. Pediatr. Surg., 12(1), 53.

TROOSKIN, STANLEY A., M.D., F.A.C.S.: DONETZ, ANTHONY P. B.S.; HARVEY, RICHARD A. Ph.D.: and GRECO, RALPH S. M.D., F.A.C.S., New Brunswick, New Jersey. "Prevention of catheter sepsis by antibiotic bonding", Surgery, 1984. pp 547-551.

HARVEY, R.A.: GRECO, R.S.: The noncovalent bonding of antibiotics to a polytetrafluoroethylene-benzalkonium graft. Ann Surg 194:642-7, 1981.

DONETZ, A.P., HARVEY, R.A., GRECO, R.S.: Stability of antibiotics bound to polytetrafluoroethylene with cationic surfactants. J Clin Microbiol 19:1-3, 1984.

Some of these prior attempts have unfortunately not produced the optimum results. The major drawback has been and remains that antimicrobial activity provided by certain surface treatments is relatively short lived. This observation has supported the theory that the agents and methods used provide only a temporary surface bonding of the selected agent to the device.

In addition, it has not been demonstrated that a treated device can be successfully sterilized by known methods without deleteriously affecting the antimicrobial agent or its bond to the surface of the material of which the device is made. That is, subsequent sterilization tends to shorten the time of antimicrobial activity.

It is therefore an objective of the present invention to provide a method by which antimicrobial or antibacterial agents can be incorporated into a wide variety of commonly used materials, so as to provide a relatively longer term protection against bacterial colonization on the surface of that material and a diminition of the problem of sepsis in implanted and long in-dwelling medical devices.

It is a further objective to provide an article exhibiting the foregoing advantages that is capable of being sterilized before use and still retain those advantages.

It is a further objective to provide an in vitro test method by which the long term performance of an infused device, made according to the present invention, can be measured.

Brief Summary of the Invention

The present invention utilizes swelling agents which are capable of increasing the micro-porosity of selected plastics or naturally occurring materials, and which are compatible with selected antimicrobial or antibacterial agents, preferably dissolving such agents without chemically altering them under conditions and in a manner to permit the infusion of the antibacterial agents selected into the swelled material uniformly and in sufficient amounts to provide for prolonged antimicrobial activity during shelf life and when the infused material is subsequently used in the body.

Brief Description of the Drawings

Fig. 1 is a schematic illustration of the perfusion apparatus described herein.

Fig. 2 is an illustration of the perfusion chamber of Fig. 1.

Fig. 3 is an illustration of the procedure for obtaining a sample of a perfused article for testing.

Fig. 4 is a pictorial illustration of the zone inhibition test for antibacterial activity used herein.

Fig. 5 is a graph of the results of antimicrobial activity over time.

Detailed Description of the Invention

The infusion treatment used herein is carried out in specially made glass impregnation chambers similar in shape to the perfusion chamber 1 illustrated in Figs. 1 and 2. These chambers typically can be long glass tubes sealed on the bottom and widened at the top to accommodate the swelling of the tubing and pump body or other device selected for infusion proceeding. The chambers are also long and wide enough to accommodate the increased length and width of the distal tubing upon swelling. These special treatment chambers are designed specifically to accommodate the device to be infused and a sufficient quantity of solution is used to provide contact between the solution and all surfaces of the device.

When open-top chambers are employed, the chambers are filled with the selected antimicrobial solution to within one inch of the upper lip of the top reservoir prior to priming the tube or other device being treated.

Charging the Material with Antimicrobial Agent

The clean, dry device to be impregnated is primed with one of the antimicrobial solutions described hereinafter, to fill the interior of the device, in this example a Denver Hydrocephalus shunt (DHS) manufactured by Denver Biomaterials, Inc. of Evergreen, Colorado, making sure all air is expelled. This step is accomplished by placing the outflow end of the distal catheter into the treatment chamber and attaching a glass syringe filled with an antimicrobial solution onto the proximal (inflow) end of the shunt by depressing the syringe plunger until no more air comes out of the

submerged distal end. In the priming of a shunt, the pump body must be held with the valve end down to assure the expulsion of air bubbles from the pump body. When all the air in the shunt has been replaced with antimicrobial solution, the proximal end is clamped approximately 0.5 inches from the end. The syringe is then removed and the shunt is submerged in the solution up to the clamp. The chamber is then filled with antimicrobial solution nearly to the top rim. A small flexible wire is then inserted approximately 0.125 inches from the proximal end so as to pierce the tube crosswise, through diametrically opposite holes. The wired end is then submerged in the antimicrobial solution and the clamp is removed. Care must be taken to submerge the tube completely at first. Then the clamp is removed so that no air enters the tube. Finally, the wire is secured to the outside of the chamber so that it holds the tube below the surface of the liquid. As the silicone rubber shunts swell in the charging solution, they become buoyant and will rise sufficiently to project out of the charging chamber if they are not properly secured with the proximal end submerged in the treatment solution.

The processing time starts when the tube is fully submerged. The chambers are covered, preferably with aluminum foil, to minimize the evaporation of the solvent from the charging solution during treatment. The duration of the treatment is preferably about 30 minutes to one hour of contact with the solution, although the swelling itself may be substantially completed in approximately 10 minutes. The charging chamber is checked visually during processing to be sure that the device has remained submerged.

At the end of the processing period the shunt is carefully pulled out of the chamber allowing the liquid

inside the shunt to drain into the chamber. The swelled silicone rubber is mechanically vulnerable at this stage and tears easily, especially at the wire in the proximal end. Therefore, it must be handled gently. After it has been removed from the charging chamber, the treated shunt is immediately immersed in a denatured ethyl alcohol bath. This rinse reduces the spotting of the antimicrobial material on the outside of the shunt as it dries, and does not noticeably reduce the level of the antimicrobial activity. The shunt is then suspended in a vertical position, pump body up, and permitted to air dry at room temperature (21°C). The shunt is then allowed to outgas in this position overnight. An elevated temperature chamber may be employed to shorten the solvent evaporation and outgassing time as long as the temperature is not so high as to degrade the antimicrobial agents deposited in the device. At room temperature the shunts will usually have regained their initial size and shape within 10 minutes after they are removed from the charging chamber.

After outgassing, the treated shunt is briefly washed in running tap water and rinsed in deionized water, just as the shunt would normally be washed during a production run. It is again dried for a short period in a warm oven at a temperature not exceeding 200°F, as higher temperatures can cause decomposition of the antimicrobials. The treated shunt is then sterilized and/or tested taking care that it is stored in the dark at room temperature. Some antimicrobials are light sensitive and can lose activity upon prolonged exposure to light and excessive heat.

The antimicrobials used to impregnate the device are best prepared in solutions immediately before use. Because of the light sensitive nature of the agents and the volatile nature of the solvent, great care must be

taken not to expose the solutions to direct sunlight or to store them in solution for any prolonged period prior to use. The solutions are discarded immediately after use.

The antimicrobials are stored in a dry form according to the manufacturers recommendations. Immediately prior to use they are weighed on an analytical balance accurate to 0.1 mg. The optimum concentrations, determined by previous testing, are about 0.1% by weight of single antimicrobials and 0.1% each by weight in combinations. The antimicrobial solutions are brought to their desired volumes in analytical grade chloroform, the preferred solvent, and stirred until they are dissolved. Only glass beakers and glass volumetric flasks are used with the chloroform-based solutions. Prior to re-use all glassware is acid-cleaned with Chromerge, a chromic-sulfuric acid solution, and rinsed copiously with tap and deionized water.

The preferred antimicrobials used in the process of the present invention are: (1) Rimactane (rifampin USP) (Ciba Pharmaceutical Company) which is a semisynthetic antibiotic derivation of rifamycin B (specifically, Rimactane is the hydrazone, 3-(4-methyl-1-piperazinyl-iminomethyl)-rifamycin SV.); and (2) Cleocin HCl (Upjohn Manufacturing Co.), which is clindamycin hydrochloride. These agents can be used singly or preferably in combination as a solute. Together they provide superior penetration, or deposition and persistent antimicrobial activity than they do when used singly in devices treated according to the present invention.

Perfusion Test of the Charged Device

To test the effectiveness of the infused products over time, samples of the shunts which have been

impregnated as described are perfused in the illustrated apparatus (Figs. 1 and 2).

Referring to Fig. 1, the perfusion chamber 1 is constructed in a shape to receive a medical device which has been infused with an antimicrobial agent or agents according to the present invention. In the embodiment shown, a Denver Hydrocephalus Shunt (DHS) with its valve and pump chamber 2 attached tubing 3 is shown. This shunt is fabricated entirely of Dow Corning silicone rubber. The perfusion chamber 1 can be shaped to accommodate any similar device equally well if the materials and methods described herein are employed. The inflow tube 5 is attached to a glass stopper 6, after passing through a multi-channel peristaltic pump 7. The glass stopper 6 is inserted in fluid-tight engagement with the open end or top of perfusion chamber 1. A side arm 10 is also provided on perfusion chamber 1 to permit outflow of fluids pumped into perfusion chamber 1 from pump 7 through tubing 5. Outflow tubing 11 is connected to side arm 10 and is provided with a valve 12. After valve 12 the outflow tubing is connected in any convenient manner to exhaust tubing 15, which in turn is attached to a reservoir 20, as shown in Fig. 1. To complete the flow path, an inflow reservoir 30 is provided which is adapted to lead the fluid composition selected for perfusion into each of the channels of the multi-channel peristaltic pump by means of manifold 31.

In addition to the foregoing, an air bleed chamber 16 is provided in the input tubing 5 between the glass stopper 6 and the multi-channel peristaltic pump 7. The air bleed chamber 16 is provided with valve means 17 fastened to the top of the chamber 16 to operate as described hereinafter to assure that the liquid level in the chamber 16, as shown, is sufficiently high to assure

covering the end of the inflow tubing 5.

The perfusion takes place as much as possible in a sterile environment, in a completely closed system, at zero head pressure, and at a rate of flow chosen to imitate the normal rate of Cerebrospinal fluid (CSF) production in the body. The system is designed to perfuse the inner and outer surfaces of the shunts or tubes simultaneously. The shunts are sampled periodically and activity-tested in the layered zone inhibition test described hereinafter.

The perfusion apparatus consists of a multiplicity of specially designed glass perfusion chambers 1, inflow and outflow reservoirs 20 and 30, a multi-channel peristaltic pump 7 (Manostat Cassette Pump) and various tubing lengths which connect inflow reservoir to pump, to chambers and finally to the outflow reservoir, see Figs. 1 and 2.

The inflow and outflow reservoirs 20 and 30 are 20-liter Nalge bottles with a outflow spigot. A glass tube plugged with loose cotton fiber at the top has been inserted through the cap of each bottle. The lower end of the tube is positioned near the interior bottom of the inflow liquid reservoir. This assures a substantially constant low head pressure no matter what the liquid level may be in each reservoir, see Fig. 1.

The Manostat Cassette pump 7 operates by a peristaltic action. Each channel can be adjusted to the desired flow rate by increasing or decreasing the flow resistance on the inflow side of the tube for that channel. The size of the tubing which fits into each cassette has been chosen to deliver a constant and predetermined flow rate at a preselected speed of the pump in the system.

The liquid flows out of the pump and into an apparatus 16, which removes any air bubbles that have

been generated by the peristaltic action before the fluid reaches the samples to be perfused. The flow proceeds out of that apparatus 16 and flows directly into the top glass stopper 6 of the perfusion chamber. The fluid then proceeds through the interior of the sample which is attached to the stopper and is submerged in the chamber. The liquid moves out of the distal end of the shunt and flows back up the outside of the sample to exit the chamber at the side arm attachment 10 near the inflow glass stopper 6 see Fig. 2. The liquid then flows into the outflow tubing 11 past a stopcock or valve 12, which enables the sampling of the eluate. The liquid then flows into a manifold 15 which feeds into the outflow reservoir 20. The inflow reservoir 30 is kept filled with sterile perfusion liquid and is never allowed to run dry. The outflow reservoir is emptied and the eluate volume is measured every 24 hours to confirm that the overall selected rate of flow in the system has been maintained. Flow can also be monitored in each channel using a Gilmont flow meter incorporated in the system, not shown.

The following preparations are made before the perfusion tests are run: (1) The samples to be perfused have, as previously described, been impregnated, outgassed, washed and then sterilized by sufficient exposure to ethylene oxide gas. (2) The chambers have been acid-cleaned and dried. (3) The perfusion tubing has been washed and steam autoclaved at 250°F and 15 psi for 20 minutes. (4) The peristaltic pump in the testing apparatus has been routinely serviced and cleaned, before perfusion.

To start the perfusion tests the input reservoir 30 and all the perfusion chambers 1 are filled and the pumping apparatus, including the associated tubing is primed with sterile perfusion liquid. The sterile

shunts to be perfused are removed from their packaging, being handled at all times with sterile rubber gloves. The shunts are primed with sterile perfusion liquid by forcing the liquid through them with a glass syringe. With all the air has been expelled from each shunt the proximal or inflow end is clamped off and is attached to inflow port on the glass stopper of the perfusion system. The distal end is submerged in the perfusion chamber during this priming operation and, as the clamp is removed from the inflow end, the pump is started to initiate flow. The glass stopper is seated in the top of the perfusion chambers and the stopcock 12 in the outflow tubing is turned to the open position. Air bubbles which may form in the pump chamber are carefully removed. The system is then allowed to run, making minor adjustments to maintain nearly constant flow, for the time of the experiment being performed. Daily maintenance of the test system, including the filling and emptying of the reservoirs, is also performed.

When distal tubing segments are perfused for testing for activity against bacteria, samples of the material being perfused are taken at varius times during the perfusion run, as shown in Fig. 3. These samples are tested in a layered zone inhibition test for antibacterial activity against Staphlococcus aureus. At the assigned sampling time each channel is sampled separately. Throughout this procedure sterile rubber gloves are used in handling the samples to maintain the sterility of the system. The outflow stopcock 12 is closed on the channel to be sampled and the glass inflow stopper 6 is lifted out of the chamber. The proximal end of the tube being sampled is removed from the glass stopper port and three 2-cm samples are cut from the tube with a sterile razor blade, see Fig. 3. These tubing samples are placed on clean but not necessarily

sterile filter paper to absorb the liquid. They are then packaged in appropriately labeled clean plastic bags. The remaining tubing is re-attached to the inflow port of the glass stopper and is resubmerged in the perfusion chamber 1. The glass stopper 6 is secured in the top of the chamber and the outflow stopcock 12 is opened. Perfusion flow is then resumed and its rate is monitored.

The samples to be tested are stored in a dark place at room temperature (21°C) until tested in the layered zone inhibition test.

In Vitro Test for Antimicrobial Activity Of the Charged Tubing

A layered zone inhibition test for antibacterial activity against Staphylococcus aureus is then performed on the samples that were removed from the perfusion apparatus. Pure cultures of Staphylococcus aureus (Oxford strain) are maintained at room temperature (21°C) in the dark in sterile cooked meat medium (Oxoid Ltd. Basingstoke, Hampshire England, Oxoid USA Inc., Columbia, Maryland).

Two days prior to use in the layered zone inhibition tests the culture is plated out on Columbia Blood Agar Base plates (Difco Laboratories, Detroit, Michigan) and allowed to grow for 24 hours in a 37°C incubator. To plate out, a drop of culture is removed from the stock aseptically with a sterile Pasteur pipette and is dropped onto a fresh Columbia Blood agar plate which has been dried for 30 minutes in a 37°C incubator. The drop is then spread on the plate with a sterile bacteriological loop to dilute and isolate the colonies.

After an 18-24 hour incubation period the plate is examined for contamination. If none is present, a discrete colony is picked off the plate with a sterile loop and is suspended aseptically in 5 ml of sterile peptone water (Difco Laboratories, Detroit, Michigan).

After overnight incubation at 37°C this solution will contain approximately 10^5 colony forming units (cfu)/ml as determined by a standard (Miles Misra) counting technique.

Preparation of Plates

The agar plates prepared for use in the layered zone inhibition test contain a prepoured bottom layer of agar which contains no bacteria. The agar used is Diagnostic Sensitivity (DST) agar (Oxoid USA, Columbia, Maryland). The agar is prepared according to the manufacturers direction (4g DST/100ml of deionized water) dissolved on a stirring hot plate and is placed in a heavy walled media bottle. The prepared bottled agar is then steam autoclaved in a pressure sterilizer for 20 minutres at 250°F and 15 psi. After autoclaving, the bottle is cooled to 56°C in a heated circulating water bath and is held for 20 minutes. The agar is then poured into clean sterile glass petri dishes, approximately 25 ml per dish. Six dishes are poured at one time (using a 6g DST/150 ml of deionized-H_2O solution). After all six have been poured the surface of each agar plate is flame-sterilized by passing the bunsen burner flame rapidly over the surface. This flaming also removes any bubbles that may have formed on the surface during pouring. The plates are cooled and stored in a refrigerator until used.

The samples to be tested have previously been treated and/or sterilized and/or perfused as described hereinbefore. Samples in the agar plate test are always sampled and tested in triplicate. The samples have been stored in a dry place, in the dark at room temperature until the zone inhibition test is set up. The samples should be removed from storage just prior to testing. They are soaked (hydrated) in sterile deionized water for one hour at room temperature prior to being embedded

in the plates.

The prepoured DST plates are removed from refrigeration and dried (as before) for approximately 20 minutes in a 37°C incubator. The plates are labeled, including the sample data, the name of the antimicrobial used and the time and date of sampling.

The agar to be used in the overlayer is prepared as before, at a concentration of 7g DST/175ml of deionized water. The agar is dissolved by stirring on a laboratory hot plate and poured into a heavy walled media bottle. The bottle is then steam autoclaved in a pressure cooker sterilizer for 20 minutes at 250°F and 15 psi. When the pressure in the sterilizer has returned to zero the bottle is removed and placed in a 56°C circulating water bath for approximatey 20 minutes. The previously prepared suspension of bacteria in peptone water is removed from the incubator. The correct number of drops of suspension are then added aseptically to the agar bottle with a sterile Pasteur pipette to bring the final concentration of bacteria in the agar to 10^5 cfu/ml. Concentration of bacteria has been determined by Miles Misra counting and the Pasteur pipettes have been calibrated to determine volume per drop.

The bacterially seeded agar is mixed gently to distribute the bacteria evenly, being careful not to generate bubbles in the solution. The solution is poured carefully onto the previously prepared dried agar plates. 175 ml of seeded solution is sufficient to overlayer 6 plates.

The samples to be tested are very quickly removed from the hydration solution with forceps. They are shaken to remove surface water and blotted on clean filter paper. The samples are then rapidly embedded in the agar-bacterial overlayer oriented radially and

placed about 120° from one another, i.e. three to a plate as shown in Fig. 4. Each sample tube is placed in the agar at a slight angle to the horizontal to facilitate the filling of the inside of the tube with liquid agar. The tubes must be placed firmly without any side to side skewing or other follow-on motion. Since diffusion of the antimicrobial agent begins immediately when the tube enters the agar, movement of the tube after it is first placed in the agar will result in nonuniform and indeterminate inhibition zones. The gar will set up within one minute after pouring onto the plate. When the plates have completely set, they are inverted and placed in an incubator for overnight culture (18-24 hours) at 37°C.

The developed plates are moved from the incubator and the zone sizes are measured as indicated in Fig. 4. The plate is held with the lid off in front of a light source and the bacterial overlayer facing the technician. The size of the zone is measured half way along the length of the tube to avoid measuring the zone producton that results from the cut ends of the tubes. The diameter of the tube (2mm in the case of distal hydrocephalus shunt tubing) is subtracted from the observed value of the zone of inhibition and this number is recorded as the zone size. The zone sizes of all three specimens on a plate are recorded. An average of those three values is taken to be the activity of the specimen against Staphlococcus aureus (in this example) for that point in time.

The results of zone measurement after infusion, perfusion and testing, as described herein, are shown in Table 1.

Referring to Table 1, it is noted that the antimicrobial agents tested included: (1) clindamycin HCl and (2) Rifampin, each at concentrations of .1% by

weight.

It can be seen that the combination of these two antimicrobial agents provides far greater antimicrobial activity after long term perfusion than does either of the individual antimicrobial agents alone, the effect being additive rather than synergistic.

Fig. 5 depicts graphically the average of the results summarized in Table 1. The graph demonstrates that the combination of .1% Rifampin plus .1% clindamycin CHl has retained nearly 75% of its activity after 28 days of continuous perfusion.

The foregoing method, article and testing clearly shows the efficacy of the combination of antimicrobials used in the infusion method described.

It is contemplated that the inventive concepts herein described may be variously otherwise embodied and it is intended that the appended claims be construed to include alternative embodiments of the invention except insofar as limited by the prior art.

TABLE 1
28 DAY PERFUSION -- ZONE SIZE (minus 2mm)
ACTIVITY AGAINST STAPHLOCOCCUS OXFORD STRAIN OVER TIME

DRUG	.1% RIFAMPIN	.2% CLIN-HCl	COMBINATION .1% RIFAMPIN .1% CLIN-HCl
0 Time	17, 19, 21	17, 21, 19, 16, 15, 14	21, 21, 22 19, 20, 21
1 Hour	19, 20, 19	14, 16, 15, 16, 16, 16	23, 23, 23 20, 20, 20
4 Hours	19, 19, 19	14, 14, 15, 14, 14	23, 23, 22, 22, 22, 22
8 Hours	16, 16, 16	13, 14, 14, 14, 14, 14	21, 21, 21, 19, 21, 19
1 Day	15, 15, 15	11, 11, 12 13, 12, 13	19, 19, 19, 21, 21, 21
3 Days	14, 13, 14	9, 9, 8 11, 11, 10	19, 18, 19, 20, 21, 20
7 Days	12, 12, 12	11, 11, 12 12, 11, 11	18, 18, 19, 18, 19, 18
14 Days	15, 14, 15	13, 12, 12, 12, 12, 11	23, 22, 22, 17, 18, 17
21 Days	11, 11, 11	5, 4, 4, 7, 7, 8	16, 17, 16, 16, 17, 17
28 Days	9, 9, 9	4, 5, 3, 5, 4, 4	15, 15, 15, 16, 15, 15

In the Claims

1. A medical device exhibiting persistent antimicrobial activity and being compatibly implantable in living tissue, wherein the surface material of said device is capable of being swelled in the presence of a swelling agent to enlarge interstitial spaces and capable of returning to an un-swelled condition upon removal of the swelling agent, said device produced by a process comprising:

a. subjecting the surface material of the device to a removable swelling agent for a time sufficient to enlarge the interstitial spaces of said surface material;

b. subjecting the resulting swollen surface material to an antimicrobial agent for a time sufficient to permit diffusion and migration thereof into the interstitial spaces of said surface material; and

c. removing the swelling agent from the surface material to cause said material to return to an un-swelled condition while retaining the antimicrobial agent therein.

2. A medical device as claimed in claim 1 wherein the swelling agent is an evaporable solvent for the antimicrobial agent, and wherein the antimicrobial agent is dissolved as solute in said swelling-agent solvent.

3. A method of infusing antimicrobials into the body of implantable, transcutaneous placable and long term in-dwelling medical devices containing silicone elastomeric surfaces comprising the steps of:

completely contacting the surface of such device with a solution comprising an evaporable swelling agent and at least one antimicrobial dissolved therein;

maintaining contact between the solution and the surface for a sufficient period of time for the solution to completely swell the elastomer and to diffuse the solution into the matrix or intersticies provided by the swelling;

evaporating the swelling agent from the solution at a temperature low enough to prevent degradation of the antimicrobials selected to thereby deposit the antimicrobial into the matrix created by the swelling agent and to return the body of said device substantially to its original physical shape and condition, rinsing the treated surface; and

sterilizing the treated surface prior to use.

4. An antimicrobial composition capable of being infused into the body of a medical device made of silicone elastomer comprising a swelling agent for the silicone elastomer, a solvent, and a solute consisting of antimicrobial agents selected from the group consisting of rifampin, clindamycin HCl and mixtures thereof.

5. The invention according to any one of the preceding claims wherein the surface material is silicone rubber.

6. The invention according to any one of the preceding claims wherein the swelling agent is chloroform.

7. The invention according to any one of the preceding claims wherein the antimicrobial agent is selected from the group consisting of rifampin, clindamycin HCl and mixtures thereof.

8. The invention according to any one of the preceding claims wherein the antimicrobial agent is dissolved in the chloroform in an amount of approximately 0.1% by weight.

9. The invention according to any one of claims 1 through 7 wherein the solute is present in the solvent in an amount of approximately from 0.1% to 0.2% by weight.

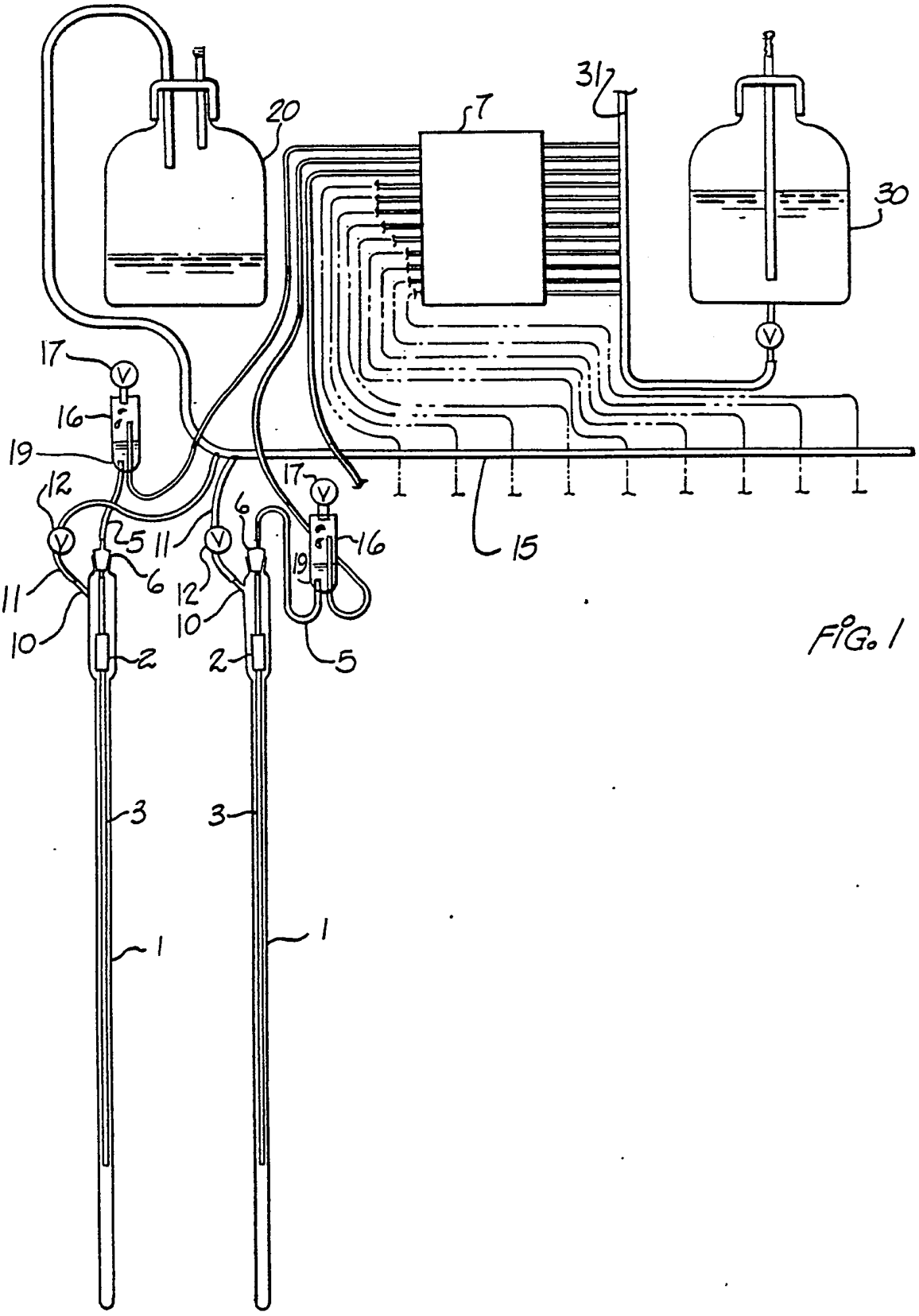

FIG. 1

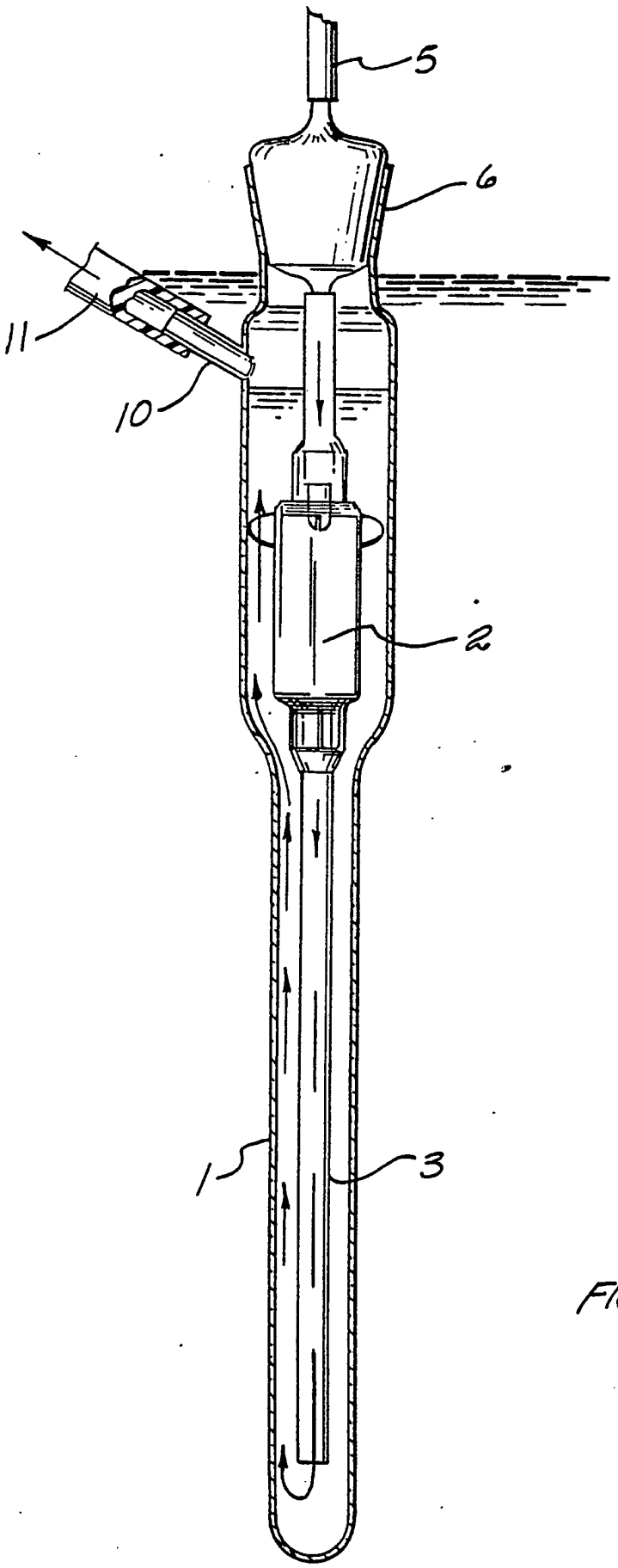

FIG. 2

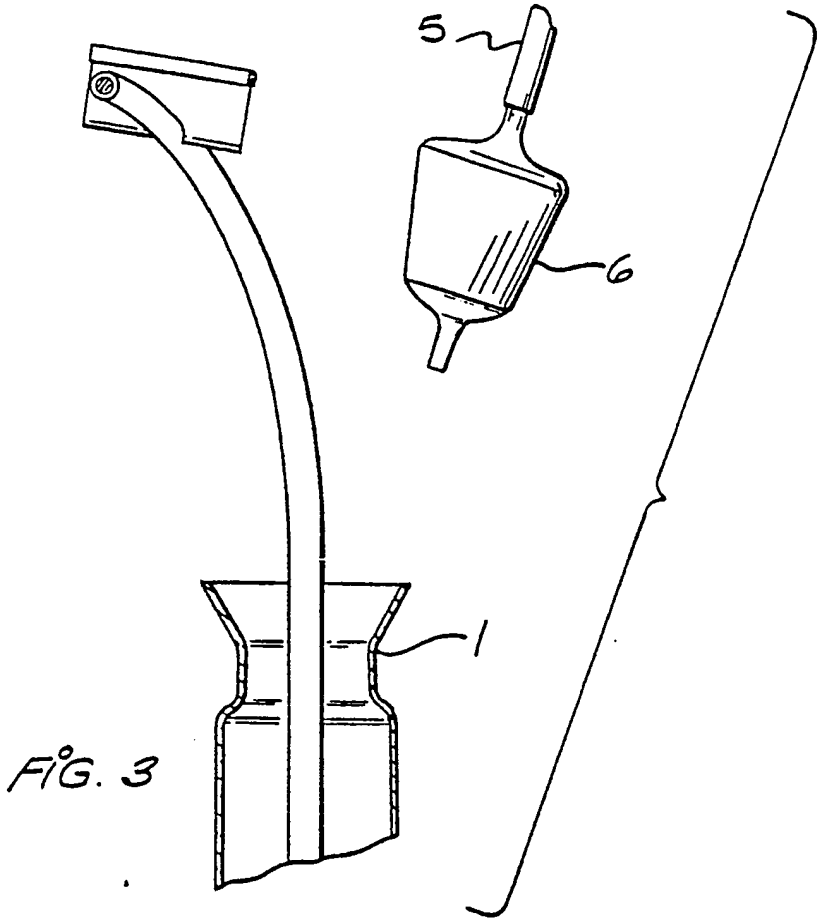

FIG. 3

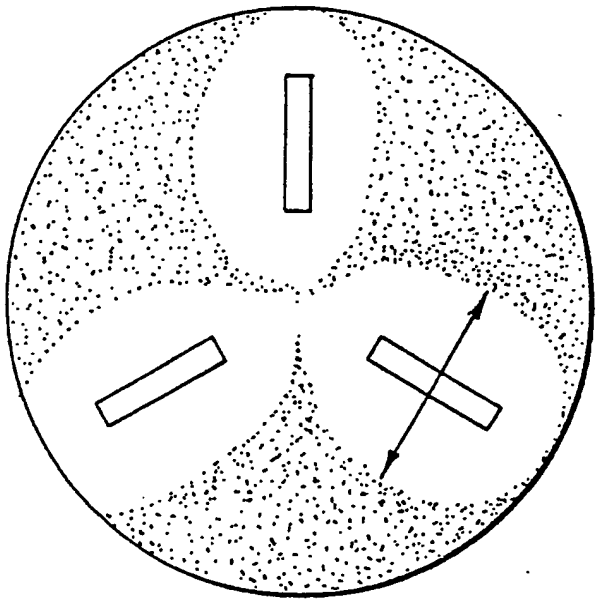

FIG. 4

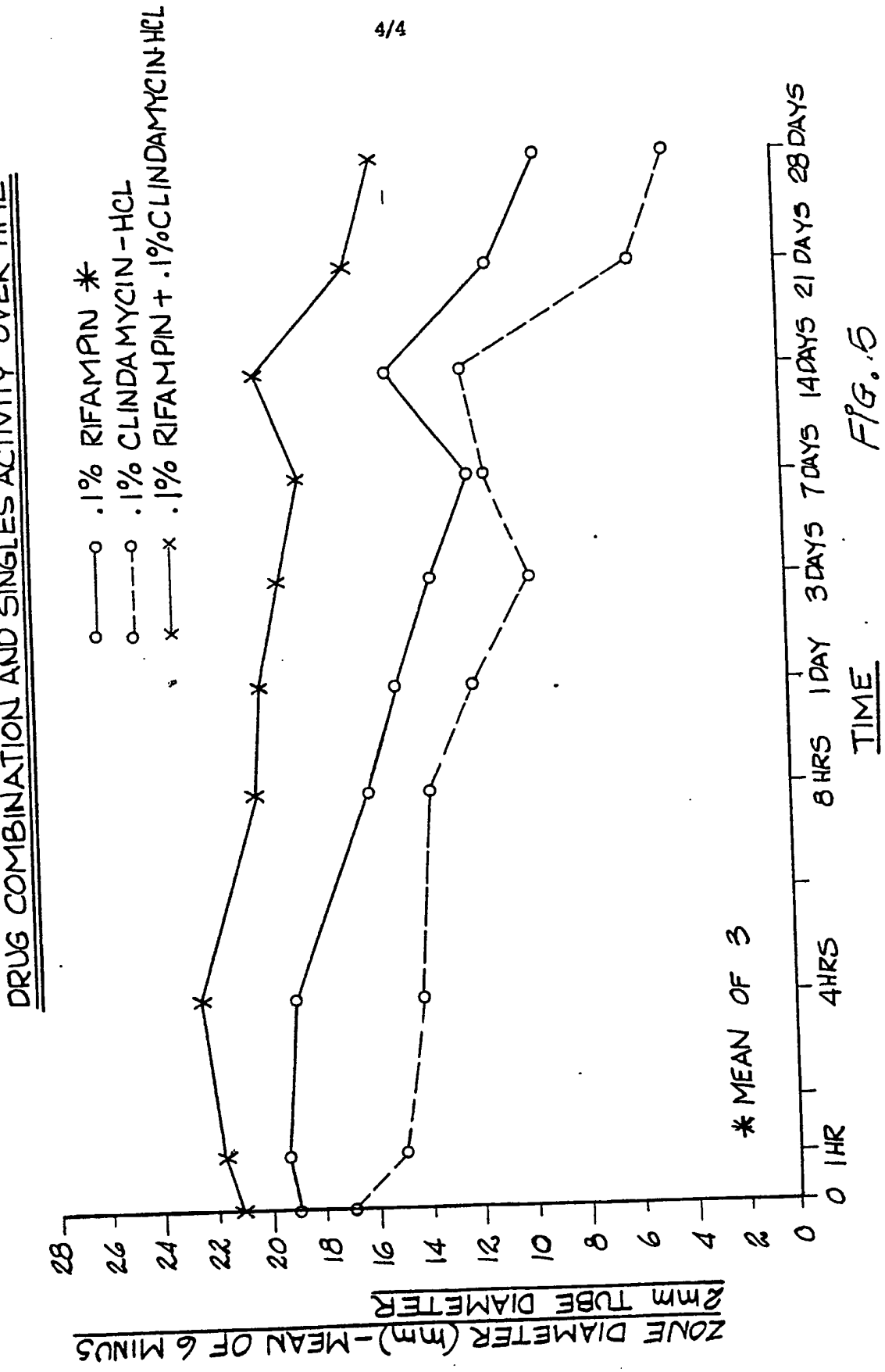
DRUG COMBINATION AND SINGLES ACTIVITY OVER TIME
.1% RIFAMPIN *
.1% CLINDAMYCIN-HCL
.1% RIFAMPIN + .1% CLINDAMYCIN-HCL
ZONE DIAMETER (mm) - MEAN OF 6 MINUS 8mm TUBE DIAMETER
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
0 1HR
4HRS
8 HRS
1 DAY
3 DAYS
7 DAYS
14 DAYS
21 DAYS
28 DAYS
TIME
* MEAN OF 3

FIG. 5

INTERNATIONAL SEARCH REPORT

International Application No PCT/US86/02668

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(4): A61M 5/32; B29B 17/00

U.S. Cl. 604/265; 264/343

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	604/265; 264/343, 344; 423/36

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X Y	US, A, 4,112,151 (COOKE) 05 September 1978. See entire document.	1,2,3 4-9
A	US, A, 4,224,736 (FELDHAKE) 30 September 1980. See entire document.	1-9
A	US, A, 4,419,322 (CLEMENCE) 06 December 1983. See entire document.	1-9
A	US, A, 4,420,514 (HUNGERFORD) 13 December 1983. See entire document.	1-9.

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
04 March 87	16 MAR 1987
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	John D. Ferros

Form PCT/ISA/210 (second sheet) (October 1981)